Furans in Synthesis. 3.[1] Furans as Terminators in Cationic Cyclization

Steven P. Tanis*[2] and Paul M. Herrinton

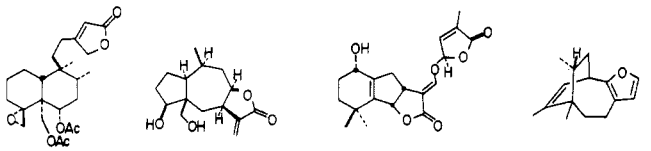
Department of Chemistry, Michigan State University, East Lansing, Michigan 48824-1322

Received April 11, 1983

3-Furylmethyl-Grignard **30** is readily coupled with a variety of ω-haloalkenes to afford the corresponding 3-substituted furan in good to excellent yields. Epoxidation of the product furyl olefins was found to be effective in producing the desired cyclization substrates only when the olefin was trisubstituted. Less highly substituted epoxy furans were prepared via the coupling of (3-furylmethyl)lithium (**43**) with ω-iodo epoxides or protected ω-iodo diols followed by closure. The cyclizations of these epoxy furans were examined with a range of Lewis acids. Treatment with $Ti(O\text{-}i\text{-}Pr)_3Cl$ and ZnI_2 led to the isolation of cyclized products **19b**, **22**, **24**, **26**, and **28** in moderate to excellent yields. Cyclization of 7,8-epoxydendrolasin (**39**) with $Ti(O\text{-}i\text{-}Pr)_3Cl$ and ZnI_2 provided 3β-hydroxypallescensin A (**49**) in 62% and 65% yields, respectively.

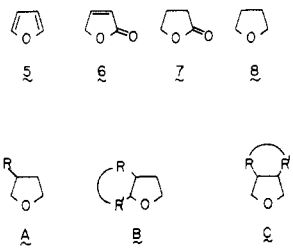
Introduction

Five-membered oxygen-containing heterocyclic rings are ubiquitous structural subunits that are observed in diverse classes of biologically active natural products.[3] This ring system is an integral part of such molecules as the insect antifeedant *ent*-neoclerodane ajugarin I (**1**),[4] the antileukemic pseudoguaianolide rudmollin (**2**),[5] the witchweed germination promoter strigol (**3**),[6] and the fish antifeedant nakafuran-8 (**4**).[7]



1 **2** **3** **4**

Compounds **1–4** represent two of the four common oxidation states of the five-membered oxygen-containing heterocyclic system. These range from the fully aromatic furan (**5**) to tetrahydrofuran (**8**). Terpenoids **1–4** also exhibit two of the three (A–C) substitution patterns observed about this ring system. Ajugarin I (**1**) illustrates the 3-substituted substructure **A** and strigol (**3**) and nakafuran-8 (**4**) possess rings fused to the 2,3-positions of the five-membered heterocycle (substructure B).



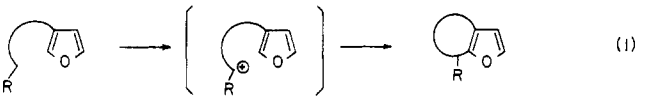
5 **6** **7** **8**

A **B** **C**

The synthesis of molecules such as **1–4** have generally been approached by a careful stereocontrolled construction of a parent carbocycle upon which the five-membered heterocycle is appended. These schemes have generally not acknowledged the basic five-membered ring nucleus as an integral part of the molecule. A truly general approach to the synthesis of molecules **1–4** should provide access to the various states of oxidation (**5–8**) as well as the different patterns of substitution (**A–C**) about the heterocyclic nucleus. Central to such an approach is the use of common intermediates which will impart regio- and stereochemical control in bond forming reactions about the periphery of the heterocycle as well as afford the desired oxidation state.

In principle the oxidation states **6–8** found in representative natural products might be prepared by the reduction[8] or oxidation[8] of a furanoid precursor **5**. Tetrahydrofuran (**8**) might result from the reduction of **5**; butenolide **6** should be available by the oxidation of **5** and in turn butyrolactone (**7**) would result from the reduction of **6**. However butenolides **6** prepared from precursor furans of substitution type **A** or **C** must be produced without regiochemical ambiguity.[9] Therefore the fully aromatic furan **5** should serve as a precursor to butenolide, butyrolactone, and tetrahydrofuran containing natural products. The synthesis of the type **A** substitution pattern, in the oxidation states **6–8** can then be simplified to the preparation of an appropriate 3-substituted furan. As we have recently reported,[1,10] the construction of various 3-substituted furans can now be readily achieved.

The type **B** structure, present in compounds **2–4** should be accessible if the propensity of furans for undergoing electrophilic attack at an α-position is considered. As illustrated in eq 1, the generation of an electron deficient



9 **10** (1)

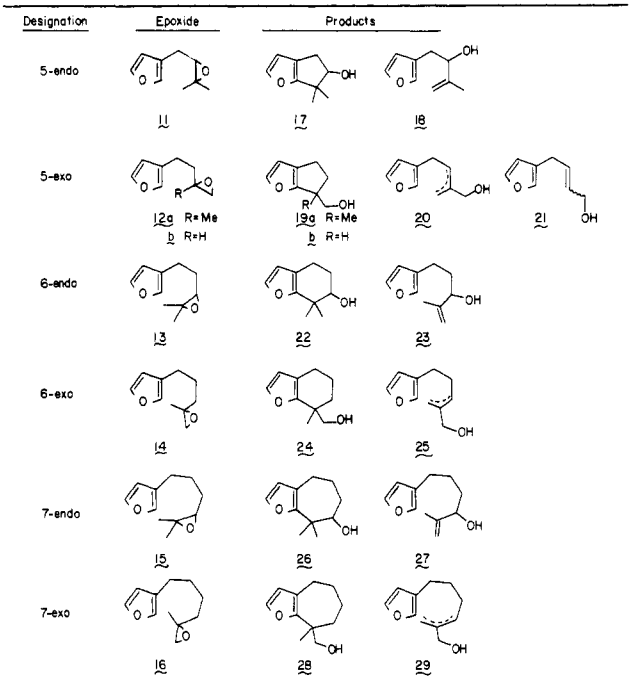
center (R) in the side chain of a 3-substituted furan, should lead to **10** after electrophilic attack and rearomatization. Therefore an efficient synthesis of the more complex type **B** substructure would be realized from the much simpler type **A** furan **9** possessing a latent electrophilic center in its side chain.

Design and Synthesis of Cyclization Substrates. Cationic cyclizations have been the object of intense study since the early 1950's.[11] However few examples have appeared in the literature in which the terminator is a furan.[8]

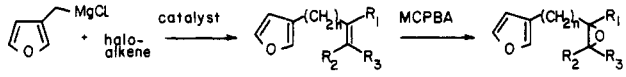
(1) For the previous report in this series see: Tanis, S. P.; Head, D. B. *Tetrahedron Lett.* **1982**, *23*, 5509.
(2) Recipient of a Camille and Henry Dreyfus Grant for Young Faculty in Chemistry 1980–84.
(3) Nakanishi, K.; et al., Eds. "Natural Products Chemistry"; Kodansha Ltd.: Tokyo, 1974.
(4) Kubo, I.; Lee, Y.-W.; Balogh-Nair, V.; Nakanishi, K.; Chapya, A. *J. Chem. Soc., Chem. Commun.* **1976**, 949.
(5) Herz, W.; Kumar, N.; Blount, J. F. *J. Org. Chem.* **1981**, *46*, 1356.
(6) Cook, C. E.; Whichard, L. P. Turner, B.; Wall, M. E.; Egley, G. H. *Science* **1966**, *154*, 1189.
(7) Schulte, G.; Scheuer, P. J.; McConnel, O. J. *Helv. Chim. Acta* **1980**, *63*, 2159.
(8) See: Katritzky, A. R.; et al., Eds. *Adv. Heterocycl. Chem.* **1982**, *30*, 167 and references cited therein.
(9) Possible solutions to this problem will be dealt with in future reports.
(10) Tanis, S. P. *Tetrahedron Lett.* **1982**, *23*, 3115.

0022-3263/83/1948-4572$01.50/0

Table I. Cyclization Substrates and Possible Products



Scheme I

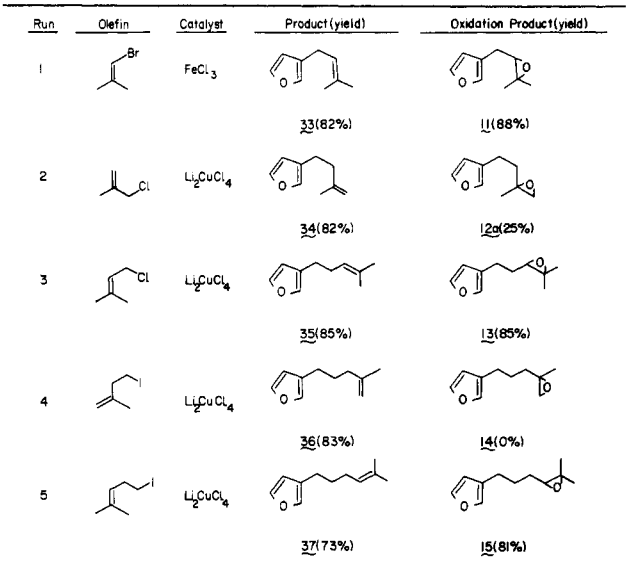


The paucity of pertinent literature precendent is likely the result of the inaccessibility of suitable substrates,[10] the poorly nucleophilic character of the furyl residue relative to standard terminator functions,[11,12] and the increased acid lability of the derived disubstituted product furan compared with the starting material.[8,12] As a result careful choice of both the initiating moiety and the reaction conditions will be required if the synthesis endeavor is to be successful.

The elegant studies of Goldsmith,[13a,b] vanTamelen,[13c-e] Boeckman,[13f] and Sharpless[13g] have shown that the epoxide function, among other groups, can be employed as the trigger for the cationic cyclization. These workers have employed a variety of Lewis acids to initiate the cyclization sequence. These relatively mild conditions coupled with the ease of epoxide introduction, either via epoxidation of a precursor olefin or insertion intact, make the epoxide the initiator of choice.

The cyclization substrates which were examined were designed to permit entry into five-, six-, or seven-membered ring systems. In order to avoid ambiguity in the choice of ring size available from a given oxirane, the epoxide function will be biased where necessary to favor one mode of C–O bond polarization over the alternative bond. This design concept is in accord with the proposed polarized nature of the intermediate.[13] We have also examined the effect of the placement of the initiating function within the ring being formed (endocyclic) or outside the forming cycle (exocyclic).[14] According to Baldwin[14] the exocyclic closures which generate five-, six-, or seven-membered rings should be favorable, while of the endocyclic closures only the formation of a six-membered ring is favorable. The required epoxyfurans and possible reaction products are illustrated in Table I.

Table II. Synthesis and Oxidation of 3-Furyl Olefins



The most obvious and at the outset simplest path to the derived epoxyfurans is outlined in Scheme I. The coupling of Grignard reagent **30**[10] with a halo alkene provides the corresponding (3-furyl) olefin **31**. Treatment of **31** with *m*-chloroperoxybenzoic acid (MCPBA) could afford epoxides **32**. Although the furyl nucleus is known to be susceptible to oxidation[8,12,15] the relative rates of furan vs. olefin attack as a function of the degree of substitution have not been reported.

As shown in Table II the coupling reactions proceed smoothly and in high yield when **30** is reacted with alkyl and allylic halides (runs **2–5**, Li_2CuCl_4 as catalyst).[10] However the synthesis of **31** (n = 1, Scheme I) requires a vinyl halide as a coupling partner. In this case anhydrous $FeCl_3$[16] (run 1, Table II) is employed as the catalyst providing an excellent yield of **33** (88%). Furyl olefins **33–37** were then each submitted to standard epoxidation conditions, 1.05 equiv of MCPBA in CH_2Cl_2 at 0 °C. As can be seen in Table II the yield of the derived epoxide is dependent upon the olefin substitution. Trisubstituted furyl alkenes **33**, **35**, and **37** give oxiranes **11**, **13**, and **15** in 81–88% yields. Furyl alkene **34** affords epoxide **12a** in

(11) See, for example: Johnson, W. S. *Acc. Chem. Res.* **1968**, *1*, 1. Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51. Johnson, W. S.; Dawson, M. I.; Ratcliffe, B. E. *J. Org. Chem.* **1977**, *42*, 153. Johnson, W. S.; McCarry, B. E.; Markezich, R.; Boots, S. G. *J. Am. Chem. Soc.* **1980**, *102*, 352. Gravestock, M. B.; Morton, D. R.; Boots, S. G.; Johnson, W. S. *Ibid.* **1980**, *102*, 800. Johnson, W. S.; McCarry, B. E.; Okorie, D. A.; Parry, R. J. *Ibid.* **1981**, *103*, 88 and references cited therein.

(12) See: (a) Dunlop, A. P.; Peters, F. N. "The Furans"; Reinhold: New York, 1953. (b) Bosshard, P.; Eugster, C. H. *Adv. Heterocycl. Chem.* **1966**, *30*, 376–491. (c) Sargent, M. V.; Crisp, T. M. In "Comprehensive Organic Chemistry"; Sammes, P. G., Ed.; Pergamon Press: Oxford, 1979; Vol 4, pp 693–744.

(13) (a) Goldsmith, D. J. *J. Am. Chem. Soc.* **1962**, *84*, 3913. (b) Goldsmith, D. J.; Phillips, C. F. *Ibid.* **1969**, *91*, 5862. (c) van Tamelen, E. E. *Acc. Chem. Res.* **1978**, *8*, 152. (d) van Tamelen, E. E.; Marson, S. A. *J. Am. Chem. Soc.* **1975**, *97*, 5614. (e) van Tamelen, E. E.; Laughhead, D. G. *J. Am. Chem. Soc.* **1980**, *102*, 869. (f) Boeckman, R. K., Jr.; Bruza, K. J.; Heinrich, G. R. *Ibid.* **1978**, *100*, 7101. (g) Morgans, D. J., Jr.; Sharpless, K. B. *Ibid.* **1981**, *103*, 462.

(14) Baldwin, J. E.; Thomas, R. C.; Kruse, L. I.; Silberman, L. X. *J. Org. Chem.* **1977**, *42*, 3846 and references cited therein.

(15) (a) Elming, N. *Adv. Org. Chem.* **1960**, *2*, 67. (b) Clauson-Kaas, N.; Limborg, F.; Fakstorp, J. *Acta Chem. Scand.* **1948**, *2*, 109. (c) Kuwajima, I.; Uvalse, H. *Tetrahedron Lett.* **1981**, *22*, 5191. (d) Gingerich, S. B.; Campbell, W. H.; Bricca, C. G.; Jennings, P. W.; Campana, C. F. *J. Org. Chem.* **1981**, *46*, 2590. (e) Takeda, K.; Minato, M.; Ishikawa, M.; Miyawaka, M. *Tetrahedron* **1964**, *20*, 2655. (f) LeGoff, E.; Williams, P. D. *J. Org. Chem.* **1981**, *46*, 4143. (g) Williams, P. D., Ph.D. Thesis, Michigan State University, 1982.

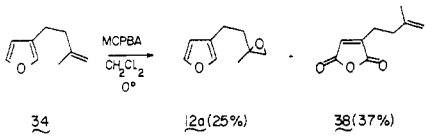
(16) Tamara, M.; Kochi. *Synthesis* **1971**, 303.

Table III. Cyclizations

epoxy furan	Lewis acid: $BF_3 \cdot OEt_2$ (0.3 equiv)	$EtAlCl_2$ (2 equiv)	Et_2AlCl (2 equiv)	Al_2O_3	$Ti(OiPr)_3Cl$ (3 equiv)	ZnI_2 (3 equiv)
11	18 (62%)		18 (85%)	18 (83%)	18 (80%)	18 (76%)
12a	20 (53%)		20 (81%)		20 (72%)	20 (70%)
12b	21 (49%)		21 (78%)		no reaction	19b (25%), 21 (44%)
13	22 (47%)	22 (16%), 23 (57%)	22 (22%), 23 (49%)	22 (32%), 23 (51%)	22 (78%)	22 (71%)
14	24 (30%), 25 (10%)	24 (0%), 25 (73%)	24 (10%), 25 (70%)	24 0%), 25 (81%)	24 (89%)	24 (70%)
15	26 (0%), 27 (41%)	26 (0%), 27 (76%)	26 (10%), 27 (69%)	26 (0%), 27 (83%)	26 (87%), 27 (8%)	26 (88%), 27 (9%)
16	28 (10%), 29 (12%)	28 (0%), 29 (64%)	28 (0%), 29 (73%)	28 (0%), 29 (79%)	28 (36%), 29 (47%)	28 (23%), 29 (52%)

a greatly reduced yield (25%) and **36** fails to give even trace quantities of **14**.

A closer examination of the oxidation of **34** (eq 2)

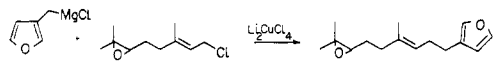


(2)

34 **12a** (25%) **38** (37%)

showed that epoxide **12a** was accompanied by anhydride **38** (37%), with 23% of alkene **34** recovered unreacted. However olefin **36**, a homologue of **34**, affords only the corresponding anhydride and unreacted **36**. Replacing MCPBA with other oxidants[17] did not lead to increased selectivity. Clearly the degree of olefin substitution has a profound effect on the product distribution. In general we have found that the protocol outlined in Scheme I is not viable if the olefin is mono- or disubstituted.

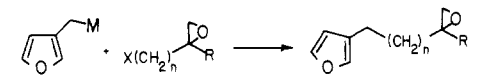
We then examined alternate routes to epoxides **12b**, **14**, and **16**. Our observation[10] that the reaction of **30** with an allylic halide possessing a potentially reactive distal epoxide function afforded only 7,8-epoxydendrolasin **39** (79%, eq 3) suggested applying this sequence to the



(3)

30 **39** (79%)

preparation of **12b**, **14**, and **16**. Epoxy iodides **40**, **41a**, and **42a** and tosylates **14b** and **42b** were each separately treated with **30** (eq 4) to provide only the products of attack at



(4)

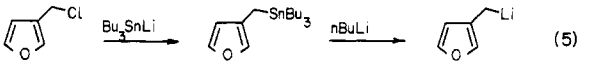
30 M=MgCl; **43** M=Li

40 X=I, n=1, R=H; **41a** X=I, n=2, R=Me; **b** X=OTs, R=Me; **42a** X=I, n=3, R=Me; **b** X=OTs, n=3, R=Me

12b n=1, R=H; **14** n=2, R=Me; **16** n=3, R=Me

the epoxide residue. Although Boeckman had demonstrated that organolithium reagents may be coupled with epoxy iodides in good yields[13f] we initially avoided employment of 3-furylmethyllithium (**43**) (eq 4) in this context. Although **43** had not, to the best of our knowledge, been reported in the literature when these studies were initiated,[18] our major concern was the possibility that the precedented allylic-type rearrangement of anion **30** would intervene resulting in electrophile capture at the adjacent α-position.[19]

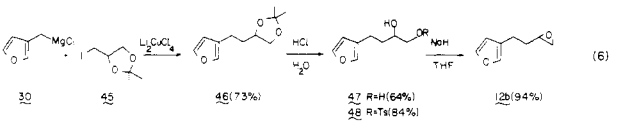
Organolithium **43** is readily prepared as described in eq 5. Treatment of 3-(chloromethyl)furan[10] with n-Bu_3SnLi[20]



(5)

44 (89%) **43**

provides stannylfuran **44** in 89% distilled yield. Tin–lithium exchange is smoothly accomplished affording a virtually quantitative yield of **43** as determined by titration. To our delight **43** reacted with iodo epoxides **41a** and **42a** in the presence of HMPA (−25 °C)[13f] to give epoxyfurans **14** and **16** in 73% and 68% yields, respectively. Products resulting from the rearranged anion or from attack at the epoxide could not be detected. However oxirane **12b** could not be prepared by this technique. As a result we were forced to take the rather circuitous route to **12b** described in eq 6. Coupling of **30** with the protected iodo diol **45** afforded furan **46** (73%), which after hydrolysis, conversion of **47** to the monotosylate **48**, and closure of the epoxide ring with NaH gave **12b** (94%).



(6)

30 **45** **46** (73%) **47** R=H (64%); **48** R=Ts (84%) **12b** (94%)

Cyclization Studies. With the desired cyclization substrates in hand the ring closing sequence was then examined. Of the myriad of Lewis acids which are available, powerfully acidic substances such as boron trifluoride etherate are often selected to catalyze epoxy olefin cyclizations. Given the relatively poor nucleophilic character of the furyl residue plus the acid lability of starting materials and desired products, the choice of Lewis acid should have a profound effect in the partitioning of the reaction between a fruitful cyclization pathway and undesired products as well as on the overall yield of these products.

Six Lewis acids were selected to determine their ability to promote epoxy furan cyclization (Table III). Other than the standard $BF_3 \cdot OEt_2$[13a-f] the choice of Lewis acids were dictated by two factors: (i) the ability to readily modify

(17) (a) *tert*-Butylhydroperoxide with $Mo(CO)_6$, $VO(acac)_2$, and $Ti(OiPr)_4$ as catalysts: Sharpless, K. B.; Michelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6138. Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63 and references cited therein. (b) H_2O_2, C_6H_5CN, NaOH: Payne, G. B.; Williams, P. H. *J. Org. Chem.* **1961**, *26*, 651.

(18) Burka has recently reported a preparation of **35** which is identical to that reported herein: Burka, L. T.; Felice, L. J.; Jackson, S. W. *Phytochemistry* **1981**, *20*, 647.

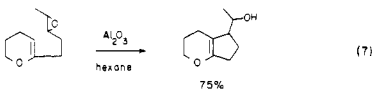
(19) Sherman, E.; Amstutz, E. D. *J. Am. Chem. Soc.* **1950**, *72*, 2195.

(20) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481.

(21) Watson, S. L.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

the potency of a group of Lewis acids with a common metal center and (ii) the possibility of moderating the Brønsted acidity of the medium through the choice of Lewis acid. Adventitious protic acid might be scavenged by a Lewis acid possessing a carbon–metal bond releasing an alkane; alternatively with proper choice of metal, the product metal–alcohol complex should be a much weaker protic acid compared to a BF_3–alcohol complex.

Snider has reported the successful application of alkyl aluminum halides as Lewis acids in acid-sensitive cyclizations. The alkyl aluminum halides cover a wide range of Lewis acidity[22] from $EtAlCl_2$, which is only slightly less potent than $AlCl_3$, to the very mild Me_3Al. Both the range of Lewis acidity presented by the alkyl aluminum halides and their ability to absorb protic acids make them likely candidates for initiating epoxy furan cyclizations. Further modification of aluminum centered Lewis acids is possible as has been demonstrated by Boeckman.[13f] Basic alumina in hexane (24 h, room temperature) was observed to successfully cyclize various epoxy vinyl ethers (eq 7) in good yields.[13f]



(7)

Titanium tetrachloride is a powerful Lewis acid which has been observed to react with epoxides to provide β-chlorotitanates.[23] The affinity of titanium for an epoxide oxygen, and likely the acidity of an alcohol–Ti complex, can be tempered by replacing chloride by alkoxy groups, such as isopropoxy. The very mild titanium tetraalkoxides have been shown to be effective in the catalysis of aldol condensations.[23] Stork[24] and Sharpless[13g] have successfully applied $Ti(O\text{-}i\text{-}Pr)_4$ to intramolecular Michael addition and α-OH-epoxide-initiated olefin cyclizations, respectively.

Zinc iodide,[25] the final Lewis acid examined in the study, was selected based on the assumption that the product zinc–alcohol complex generated during the course of the cyclization would be a weak protic acid. The correctness of this supposition is illustrated by Marshall's successful closure of an acid-labile diene-aldehyde during his synthesis of occidentalol.[25a]

The substrate epoxy furans were then submitted to cyclization conditions as follows. Oxirane **11** was initially subjected to the "standard" conditions for polyene cyclizations, 0.33 equiv of $BF_3{\cdot}OEt_2$[13] in CH_2Cl_2 at −25 °C. As anticipated **11** failed to yield the cyclized product **17**, instead 62% of allylic alcohol **18** was obtained. Epoxy furans **12a**, **12b**, **13**, **14**, **15**, and **16** were then treated with $BF_3{\cdot}OEt_2$ in a similar fashion (Table III). Only the six-membered endocyclic precursor **13** and the 6-*exo*-epoxy furan **14** provided appreciable quantities of cyclized products, leading to **22** and **24** in 47% and 30% yields, respectively. The majority of the materials recovered from the attempted cyclizations of **12a**, **12b**, **15**, and **16** were the corresponding allylic alcohols. In all of these cases the material balance was poor with only about 60% of the starting mass recovered. The general lack of cyclization, coupled with the poor mass balance, clearly demonstrates that the standard cyclization conditions are not generally applicable.

A study of aluminum base Lewis acids in the cyclization of epoxy furans began with $EtAlCl_2$, and Et_2AlCl. Treatment of epoxy furans **11–16** with two equiv of either $EtAlCl_2$ or Et_2AlCl, in CH_2Cl_2 at −25 °C, provided little cyclized materials (Table III). As with $BF_3{\cdot}OEt_2$ only the 6-*endo*-epoxide **13** yielded appreciable quantities of cyclized products, 16% and 22%, respectively. Smaller quantities of **24** (10%) and **26** (10%) were isolated after treatment of **14** and **15** with Et_2AlCl. However, as is obvious from an inspection of Table III, this modification of the Lewis acid has resulted in marked improvement in the mass balance.

The results from these cyclization attempts demonstrated the majority of the substrate was being diverted to undesired elimination products. Therefore further moderation of the Lewis acid was required. Stirring epoxy furans **11** and **13–16** with alumina resulted in very high yields (60–90%) of elimination products. Only substrate **13** afforded cyclized product, and **22** was obtained in 32% yield. Again elimination was preferred over cyclization in all of the cases examined.

In the titanium series $Ti(O\text{-}i\text{-}Pr)_4$ was initially examined as a Lewis acid in attempted cyclizations of epoxides **11–16**. Exposure of these substances to 3 equiv of $Ti(O\text{-}i\text{-}Pr)_4$ in CH_2Cl_2 for extended periods at room temperature resulted in quantitative starting material recovery.

The next most acidic compound in this series $Ti(O\text{-}i\text{-}Pr)_3Cl$, prepared by the disproportionation of 3 equiv of $Ti(O\text{-}i\text{-}Pr)_4$ with 1 equiv of $TiCl_4$[23] (1.5 M in CH_2Cl_2), proved to be an efficient and useful promoter of epoxy furan cyclization. As before oxiranes **11** and **12a** provided only products of elimination, allylic alcohols and **18** (80%) and **20** (72%), respectively. Epoxide **12b** could not be induced to react, even after exposure of 3 equiv of $Ti(O\text{-}i\text{-}Pr)_3Cl$ (CH_2Cl_2) at room temperature after 24 h. Similar treatment of epoxy furan **13** led to the formation of the desired cyclized adduct **22** in 78% yield virtually uncontaminated by elimination products. 6-*exo*-Epoxide **14** and 7-*endo*-precursor **15** afforded excellent yields of cyclized products **24** (89%) and **26** (87%), respectively, the latter being accompanied by a modest amount of allylic alcohol **27** (8%). Even epoxide **16**, designated as 7-exo, gave a respectable yield of cyclic product **28** (36%) when exposed to $Ti(O\text{-}i\text{-}Pr)_3Cl$.

Cyclizations of furyl epoxides **11–16** with ZnI_2, the final Lewis acid in this study were performed in CH_2Cl_2 at room temperature. Exposure of furyl epoxides **11** and **12a** to 3 equiv of freshly prepared ZnI_2 led to the isolation of high yields of the derived allylic alcohols (Table III). However furyl epoxide **12b** afforded the elusive five-membered cyclic product **19b**, albeit in 25% yield upon exposure to ZnI_2. Epoxy furans **13–16** provided good to excellent yields of the corresponding cyclic products accompanied by small quantities of allylic alcohols.

A more rigorous test of the epoxy furan cyclization as a route to naturally occurring terpenoids might require the formation of two or more rings during the sequence. Pallescensin-A (**50**)[28] provided the appropriate test. Epoxydendrolasin (**39**)[10] (eq 3) provides 3β-OH pallascensin-A (**49**)[29] in 47% yield upon treatment with $BF_3{\cdot}OEt_2$ (eq 8).

(22) (a) Snider, B. B.; Rodini, D. J.; Karras, M.; vanStraten, J. *Tetrahedron* **1981**, *37*, 3927. (b) Snider, B. B.; Rodini, D. J.; vanStraten, J. *J. Am. Chem. Soc.* **1980**, *102*, 5872.

(23) Feld, R.; Cowe, D. L. "The Organic Chemistry of Titanium"; Butterworths: Washington DC, 1965 and references cited therein.

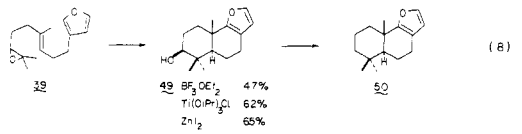
(24) Stork, G.; Shiner, C. S.; Winkler, J. D. *J. Am. Chem. Soc.* **1982**, *104*, 310.

(25) (a) Marshall, J. A.; Wuts, P. G. M. *J. Org. Chem.* **1977**, *42*, 1794. (b) Reetz, M. T.; Hüttenhain, S.; Hübner, F. *Synth. Commun.* **1981**, *11*, 217.

(26) Sutherland, J. K. *Chem. Soc. Rev.* **1980**, *9*, 265. Hashimoto, S.; Itoh, A.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 4192.

(27) We are currently investigating the synthesis and reactions of RS- and R_3SiO-substituted variants of **30** and **43**.

(28) Cimino, G.; DeStefano, S.; Guerriero, A.; Minale, L. *Tetrahedron Lett.* **1975**, 1417; **1975**, 1425.



(8)

Zinc iodide and triisopropoxytitanium chloride provide higher yields of **49**, 62% and 65%, respectively, as well as a cleaner reaction mixture. Compound **49** was smoothly converted to pallescensin-A (**50**) as described by Nasipuri.[29]

Our results (Table III) clearly demonstrate the potential of the epoxy furan cyclization for the formation of six- and seven-membered rings. Good to excellent yields of cyclic products can be realized with a judicious choice of Lewis acid. However, closure to form five-membered rings remains problematic. As anticipated, the 5-endo type of closure, represented by epoxide **11**, afforded only elimination products. In this case the overlap necessary for cyclization is precluded by the presence of but a single sp^3 carbon in the forming cycle. The low yield of cyclized product **19b** from 5-*exo*-epoxide **12b** was initially disappointing. There is ample literature precendent for cyclizations to form five-membered rings with similar steric constraints,[13f,22b,26] but in each of these cases the terminator function is considerably more nucleophilic than a furan (eq 7). A simple solution, in principle, to this problem is to increase the nucleophilicity of the furyl terminator by the introduction of a substituent onto the furan ring which can donate electron density.[27] Unfortunately few examples of stable, appropriately substituted furans related to organometallics **30** and **43** are known.[27]

Experimental Section

General. Tetrahydrofuran (THF) was dried by distillation, under nitrogen from sodium benzophenone ketyl; methylene chloride was dried by distillation under nitrogen from calcium hydride; *N,N*-dimethylformamide (DMF) was dried by distillation at reduced pressure from phosphorous pentoxide; hexamethylphosphoramide (HMPA) was dried by distillation at reduced pressure from calcium hydride; pyridine was dried by distillation, under nitrogen, from calcium hydride; diisopropylamine was dried by distillation, under nitrogen, from calcium hydride. Petroleum ether refers to 30–60 °C boiling point fraction of petroleum benzin. Diethyl ether was purchased from Mallinkrodt, St. Louis, MO, and used as received. *n*-Butyllithium in hexane was purchased from Aldrich, Milwaukee, WI, and titrated by the method of Watson and Eastham.[21] Ethylaluminum dichloride and diethylaluminum chloride were purchased as hexane solutions from Alfa Products, Danvers, MA, and used as received. Magnesium metal turnings were activated by successive washings with 1 N aqueous hydrochloric acid, water, acetone, and ether and dried in a dessicator over phosphorous pentoxide at reduced pressure. All other reagents were used as received unless otherwise stated; all reactions were carried out under a blanket of argon with the rigid exclusion of moisture from all reagents and glassware unless otherwise mentioned.

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Pye-Unicam SP-1000 infrared spectrophotometer with polystyrene as standard. Proton magnetic resonance spectra were recorded on a Varian T-60 at 60 MHz or a Bruker WM-250 spectrometer at 250 MHz as indicated, as solutions in deuteriochloroform unless otherwise indicated. Chemical shifts are reported in parts per million of the δ scale relative to a tetramethylsilane internal standard. Data are reported as follows: chemical shift (multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (Hz), integration). ^{13}C magnetic resonance spectra were recorded on a Bruker WM-250 spectrometer (68.9 MHz) and are reported in parts per million from tetramethylsilane on the δ scale. Electron impact (EI/MS) and chemical ionization (CI/MS) mass spectra were recorded on a Finnigan 4000 with an INCOS 4021 data system. Elemental analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI.

Flash chromatography was performed according to the procedure of Still et al.[30] by using the Whatman silica gel mentioned and eluted with the solvents mentioned. The column outer diameter (od) is listed in millimeters.

2-Methyl-4-(3-furyl)but-2-ene (33). To activated magnesium metal turnings (0.243 g, 10 mmol) covered by THF (15 mL) was added (3-furyl)chloromethane (1.16, 10 mmol) in one portion. The mixture was allowed to stir at room temperature until all the magnesium had been consumed (about 1 h). The resulting golden solution was cooled to 0 °C and 1-bromo-2-methylpropene[31] (1.35 g, 10 mmol) was added in one portion followed immediately by anhydrous $FeCl_3$ (16 mg, 0.01 mmol). The resulting deep red reaction mixture was stirred at 0 °C for 1 h and then was cast into saturated aqueous NH_4Cl (100 mL) and ether (100 mL). The organic phase was separated, washed with water (100 mL) and brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo to yield a golden liquid. The crude product was purified by chromatography on a column of silica gel (230–400 mesh, 100 g, 50 mm od, ether–petroleum ether 1:99, 30-mL fractions) by using the flash technique. Fractions 6–9 provided 1.12 g, 82%, of **33** as a colorless liquid: ^1H NMR (250 MHz) δ 7.22 (t, J = 2 Hz, 1 H), 7.04 (m, 1 H), 6.13 (br s, 1 H), 4.54 (t, J = 10 Hz, 1 H), 3.10 (d, J = 10 Hz, 2 H), 2.62 (s, 3 H), 2.50 (s, 3 H); IR (neat) 2900, 1500, 1450, 1375, 1155, 1070, 1010, 870, 780 cm^{-1}; EI/MS (70 eV) 136 (M^+, base), 121 (42), 93 (41), 91 (37), 77 (36).

General Procedure for Preparation of 3-Furyl Olefins, 2-Methyl-4-(3-furyl)but-1-ene (34). To activated magnesium metal turnings (0.243 g, 10 mmol) covered by THF (15 mL) was added (3-furyl)chloromethane[10] (1.16 g, 10 mmol) in one portion. The mixture was stirred at room temperature until all the magnesium had been consumed (about 1 h). The resulting golden solution was cooled to 0 °C in an ice–water bath and 3-chloro-2-methylpropene[32] (0.90 g, 10 mmol) was added followed immediately by Li_2CuCl_4 (0.12 mL, 0.1 M in THF). The reaction mixture immediately warmed and turned black. After the solution had been stirred at 0 °C for 30 min, it was cast into saturated aqueous NH_4Cl (100 mL) and ether (100 mL). The organic phase was separated, washed with water (100 mL) and brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo to yield a colorless liquid. The crude product was purified by chromatography on a column of silica gel (230–400 mesh, 100 g, 50 mm od, ether–petroleum ether 1:99, 30 mL fractions) using the flash technique. Fractions 6–11 provided 1.10 g, 81%, of **34** as a colorless liquid: ^1H NMR (250 MHz) δ 7.28 (t, J = 1.8 Hz, 1 H), 7.13 (m, 1 H), 6.19 (br s, 1 H), 4.62 (br s, 2 H), 2.27 (m, 4 H), 1.76 (d, 3 H); IR (neat) 2950, 2870, 1500, 1150, 1080, 1025, 900, 890, 780 cm^{-1}; EI/MS (70 eV) 136 (M^+, 15), 121 (11.7), 94 (46.7) 81 (base).

2-Methyl-5-(3-furyl)pent-1-ene (36). Grignard reagent **30** (10 mmol) was reacted with 1.96 g (10 mmol) of 4-iodo-2-methyl-1-butene[33] according to the general procedure for the preparation of 3-furyl olefins to provide 1.24 g, 83%, of **36** as a colorless liquid: ^1H NMR (250 MHz) δ 7.25 (t, 1.8 Hz, 1 H), 7.08 (m, 1 H), 6.15 (br s, 1 H), 4.72 (br s, 2 H), 2.39 (m, 4 H), 1.98 (m, 2 H), 1.68 (s, 3 H); IR (neat) 2930, 2865, 1500, 1150, 1070, 1025, 900 cm^{-1}; EI/MS (70 eV) 150 (M^+, 19.2), 122 (10.0), 107 (9.8), 95 (15.6), 94 (97), 82 (76.4), 81 (base).

2-Methyl-6-(3-furyl)hex-2-ene (37). Grignard reagent **30** (10 mmol) was reacted with (2.10 g, 10 mmol) 5-iodo-2-methyl-2-pentene[34] according to the general procedure outlined above to provide 1.19 g, 73%, of **37** as a colorless liquid: ^1H NMR (250 MHz) δ 7.29 (t, J = 2 Hz, 1 H), 7.16 (m, 1 H), 6.20 (s, 1 H), 5.18 (t, J = 6 Hz, 1 H), 2.38 (t, J = 6 Hz, 2 H), 2.36–1.03 (m, 4 H), 1.64 (s, 3 H), 1.58 (s, 3 H); IR (neat) 2950, 2880, 1500, 1160, 1070,

(29) Nasipuri, D.; Das, G. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2776. Nasipuri has examined the cyclization of **39** with BF_3·OEt_2 and has reported obtaining **49** in 23% yield.

(30) Still, W. C.; Mitra, A.; Khan, M. *J. Org. Chem.* **1978**, *41*, 2923.
(31) Braude, E. A.; Evans, E. A. *J. Chem. Soc.* **1955**, 3324.
(32) Purchased from Aldrich Chemical Co.
(33) Trost, B. M.; Konz, R. A. *J. Org. Chem.* **1974**, *39*, 2475.
(34) McCormick, J. P.; Barton, D. L. *J. Chem. Soc., Chem. Commun.* **1975**, 303.

1025, 905, 865, 780 cm^{-1}; EI/MS (70 eV) 164 (M$^+$, 2) 149 (3), 121 (9.1), 108 (8), 94 (14), 82 (base).

General Procedure for Epoxidation of 3-Furyl Olefins. Preparation of 2-Methyl-4-(3-furyl)-2,3-epoxybutane (11). To a magnetically stirred solution of **33** (1.36 g, 10 mmol) in methylene chloride (30 mL), cooled to 0 °C in an ice–water bath, was added a solution of *m*-chloroperoxybenzoic acid (2.32 g, 11 mmol, 85%) in methylene chloride (50 mL) over a period of 30 min. The resulting mixture was stirred at 0 °C for 30 min, the suspension was then filtered, and the filtrate cast into 10% aqueous sodium bisulfite (150 mL) and ether (200 mL). The organic phase was separated, washed with saturated aqueous $NaHCO_3$ (100 mL), water (100 mL) and brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo to yield a light yellow liquid. The crude product was purified by chromatography on a column of silica gel (60–230 mesh, 75 g, 50 mm od, ether–petroleum ether 1:4, 40-mL fractions) by using the flash technique. Fractions 6–11 provided 1.33 g, 88%, of **11** as a colorless liquid: ^{1}H NMR (250 MHz) δ 7.42 (t, J = 2.8 Hz, 1 H), 7.27 (s, 1 H), 6.30 (s, 1 H), 2.89 (t, J = 6 Hz, 1 H), 2.70 (dq, J = 6, 12 Hz, 2 H), 1.42 (s, 3 H), 1.40 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 144.4, 140.7, 122.0, 112.35, 69.49, 59.77, 26.24, 26.06; IR (neat) 2965, 2925, 1500, 1445, 1375, 1155, 1125, 1020, 870, 780, 760 cm^{-1}; EI/MS (70 eV) 152 (M$^+$, 4.5), 137 (base), 123 (6.8), 108 (29).

2-Methyl-4-(3-furyl)-1,2-epoxybutane (12a). **34** (1.3 g, 10 mmol) was treated with *m*-chloroperoxybenzoic acid (MCPBA) (2.02 g, 10 mmol, 85%) according to the general procedure for epoxidation of 3-furyl olefins to provide 0.38 g, 25%, of **12a** as a clear colorless liquid: ^{1}H NMR (250 MHz) δ 7.21 (t, J = 2 Hz, 1 H), 7.09 (m, 1 H), 6.23 (br s, 1 H), 2.53 (m, 4 H), 1.83 (m, 2 H), 1.38 (s, 3 H); IR (neat) 2930, 2860, 1500, 1450, 1430, 1390, 1175, 1030, 890 cm^{-1}; EI/MS (70 eV) 156 (M$^+$, 54.6), 139 (84.3), 121 (43.13), 112 (63.10), 96 (48.7), 81 (67.0), 55 (base).

2-Methyl-5-(3-furyl)-2,3-epoxypentane (13). **35**[10] (1.50 g, 10 mmol) was treated with MCPBA (2.02 g, 10 mmol, 85%) according to the general procedure for epoxidation of 3-furyl olefins to provide 1.40 g, 85%, of **13** as a clear colorless liquid: ^{1}H NMR (250 MHz) δ 7.39 (t, J = 2 Hz, 1 H), 7.22 (s, 1 H), 6.29 (s, 1 H), 2.78 (t, J = 6 Hz, 1 H), 2.56 (m, 2 H), 1.78 (dd, J = 6, 6 Hz, 2 H), 1.32 (s, 3 H), 1.21 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 155.8, 141.4, 114.16, 110.00, 76.59, 37.81, 28.64, 24.10, 21.20, 18.99; IR (neat) 2980, 2940, 2880, 1500, 1440, 1380, 1160, 1115, 1025, 925, 875, 790 cm^{-1}; EI/MS (70 eV) 166 (M$^+$, 7.1), 151 (12), 133 (10), 123 (13.4), 108 (42.8), 95 (39.4), 85 (75.0), 81 (83.4), 72 (38.5), 59 (base). Anal. Calcd for $C_{10}H_{16}O_2$: C, 72.29; H, 8.43. Found: C, 72.25; H, 8.51.

2-Methyl-6-(3-furyl)-2,3-epoxyhexane (15). **37** (1.64 g, 10 mmol) was reacted with MCPBA (2.02 g, 10 mmol, 85%) according to the general procedure for the epoxidation of 3-furyl olefins to epoxides to provide 1.45 g, 81%, of **15** as a clear colorless liquid: ^{1}H NMR (250 MHz) δ 7.28 (t, J = 2 Hz, 1 H), 7.18 (t, J = 2 Hz, 1 H), 6.21 (br s, 1 H), 2.67 (t, J = 6 Hz, 1 H), 2.45 (m, 2 H), 1.58 (m, 4 H), 1.22 (s, 3 H), 1.18 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 157.6, 140.2, 114.4, 109.6, 75.81, 38.62, 29.43, 23.21, 24.1, 20.65, 19.34; IR (neat) 2980, 2950, 2880, 1500, 1440, 1390, 1150, 1115, 1020, 915, 875, 790, 720 cm^{-1}; EI/MS (70 eV) 180 (M$^+$, 1.7), 151 (7.4), 135 (5.6), 121 (14), 107 (11.3), 98 (2), 94 (base). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.33; H, 8.89. Found: C, 73.40; H, 8.95.

((Tri-*n*-butylstannyl)methyl)furan (44). To a solution of diisopropylamine (4.44 g, 44 mmol) in anhydrous THF (50 mL) cooled to 0 °C in an ice–water bath was added *n*-butyllithium (1.7 N, 25.8 mL, 44 mmol) over a period of 10 min, and the mixture was allowed to stir for an additional 10 min after the addition was complete. To the resulting solution was added tri-*n*-butyltin hydride (11.6 g, 40 mmol) over a period of 10 min and the mixture allowed to stir for an additional 15 min and then cooled to −25 °C in a dry ice–carbon tetrachloride bath. To the resulting yellow solution was added (3-furyl)chloromethane (4.66 g, 40 mmol) over a period of 10 min. The cooling bath was removed and the reaction allowed to stir and warm to room temperature over 1 h. The mixture was then cast into ether (300 mL) and saturated aqueous NH_4Cl (200 mL). The organic phase was separated, washed with water (200 mL) and brine (200 mL), dried (Na_2SO_4), and concentrated in vacuo to yield a yellow liquid. Distillation provided 13.15 g, 89% of **44** as a colorless liquid: bp (0.05 mm) 125 °C (lit.[18] bp 116–119 °C (0.55 mm)); ^{1}H NMR (60 MHz) δ 7.23 (t, J = 2 Hz, 1 H), 7.18 (m, 1 H), 6.21 (s, 1 H), 2.0–0.7 (m, 29 H); EI/MS (70 eV) 372 (1.3), 355 (6), 315 (10), 291 (28), 235 (32), 201 (19), 179 (base).

2-Methyl-5-(3-furyl)-1,2-epoxypentane (14). To a solution of **44** (1.85 g, 5 mmol) in THF (5 mL) cooled to −78 °C in a dry ice–2-propanol bath was added *n*-butyllithium (3.3 mL, 5 mmol, 1.51 M in hexane) over a period of 5 min. The solution was stirred at −78 °C for an additional 10 min and then HMPA (0.90 g, 5 mmol) was added in one portion. The resulting red solution was transferred via cannula into a solution of **41a** (1.06 g, 5 mmol) in THF (10 mL) which was cooled to −25 °C in a dry ice–carbon tetrachloride bath. The cooling bath was removed and the mixture stirred at room temperature overnight. The solution was cast into saturated aqueous NH_4Cl (100 mL) and ether (100 mL). The organic phase was separated, washed with water (100 mL) and brine (100 mL) dried (Na_2SO_4), and concentrated in vacuo to yield a yellow liquid. The crude product was purified by chromatography on a column of silica gel (230–400 mesh, 75 g, 40 mm od, ether–petroleum ether 1:4, 25-mL fractions) by using the flash technique. Fractions 12–17 provided 0.60 g, 73%, of **14** as a clear colorless liquid: ^{1}H NMR (250 MHz) δ 7.32 (t, J = 2 Hz, 1 H), 7.20 (m, 1 H), 6.22 (m, 1 H), 3.18 (m, 2 H), 2.76–2.50 (m, 2 H), 1.77–1.51 (m, 2 H), 1.32 (s, 3 H); IR (neat) 2925, 2860, 1500, 1450, 1390, 1160, 1070, 1025, 975, 905, 890 cm^{-1}; EI/MS (70 eV) 166 (M$^+$, 2.3), 149 (8.1), 141 (19), 135 (8.6), 129 (7.8), 121 (12.0), 109 (17.6), 94 (base). Anal. Calcd for $C_{10}H_{16}O_2$: C, 72.29; H, 8.43. Found: C, 72.25; H, 8.51.

2-Methyl-6-(3-furyl)-1,2-epoxyhexane (16). To a solution of **44** (1.85 g, 5 mmol) in THF (5 mL) cooled to −78 °C in a dry ice–2-propanol bath was added *n*-butyllithium (3.3 mL, 5 mmol, 1.51 M in hexane) over a period of 5 min. The solution was stirred at −78 °C for 10 min, HMPA (0.896 g, 5 mmol) was then added in one portion, and the mixture was stirred at −78 °C for an additional 10 min. The resulting solution was transferred via cannula to a solution of **42a** (1.12 g, 5 mmol) in THF (10 mL) cooled to −25 °C in a dry ice–carbon tetrachloride bath. The cooling bath was removed and the mixture was allowed to stir at room temperature overnight. The solution was cast into saturated aqueous NH_4Cl (100 mL) and ether (150 mL). The organic phase was separated, washed with water (100 mL) and brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo to yield a yellow liquid. The crude product was purified by chromatography on a column of silica gel (230–400 mesh, 75 g, 40 mm od, ether–petroleum ether 1:4, 25-mL fractions) by using the flash technique. Fractions 8–13 afforded 0.612 g (68%) of **16** as a colorless liquid: ^{1}H NMR (250 MHz) δ 7.36 (t, J = 2 Hz, 1 H), 7.21 (t, J = 2 Hz, 1 H), 6.24 (br s, 1 H), 3.90 (t, J = 9 Hz, 1 H), 3.28 (m, 1 H), 2.58 (m, 2 H), 2.42 (t, J = 9 Hz, 2 H), 1.66–1.38 (m, 4 H), 1.31 (s, 3 H); IR (neat) 3010, 2990, 2925, 1540, 1500, 1445, 1380, 1150, 1110, 1070, 900, 805, 780 cm^{-1}; EI/MS (70 eV) 180 (M$^+$, 12), 163 (11), 149 (14.4), 135 (28), 121 (18.7), 108 (60), 82 (base). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.33; H, 8.89. Found: C, 73.21; H, 8.96.

1,2-Di-*O*-isopropylidene-4-(3-furyl)butane-1,2-diol (46). To an activated magnesium metal turnings (0.73 g, 30 mmol) covered by THF (40 mL) was added (3-furyl)chloromethane (3.5 g, 30 mmol) and the mixture stirred at room temperature until the magnesium was consumed (about 2 h). The resulting golden solution was cooled to 0 °C in an ice–water bath and **45**[36] (6.05 g, 25 mmol) was added in one portion followed immediately by Li_2CuCl_4 (0.2 mL, 0.1 M in THF). The mixture was stirred at room temperature for 6 h and then was cast into saturated aqueous NH_4Cl (150 mL) and ether (150 mL). The organic phase was separated, washed with 10% aqueous sodium bisulfite (100 mL), water (100 mL), and brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo to provide a yellow liquid. The crude product was purified by chromatography on a column of silica gel (230–400 mesh 110 g, 50 mm od, ether–petroleum ether 5:95, 40-mL fractions) by using the flash technique. Fractions 18–29 provided 3.57 g, 73%, of **46** as a clear colorless liquid: ^{1}H NMR (60 MHz) δ 7.28 (t, J = 2 Hz, 1 H), 7.19 (m, 1 H), 6.22 (br s, 1 H), 4.06 (t, J = 6.5 Hz, 1 H), 3.98 (t, J = 6.5 Hz, 1 H), 3.40 (m, 1 H), 2.52

(35) Mori, K.; Kobayashi, S.; Matsui, M. *Agri. Biol. Chem.* **1975**, *39*, 1889.

(36) Fischer, E.; Pfahler, E. *Ber. Dtsch. Chem. Ges.* **1920**, *53*, 1606.

(m, 2 H), 1.87 (m, 2 H), 1.42 (s, 3 H), 1.33 (s, 3 H); IR (neat) 2990, 2950, 2880, 1500, 1365, 1240, 1165, 1080, 1025, 890, 780 cm^{-1}; EI/MS (70 eV) 196 (M^+, 4.43), 181 (4.33), 138 (5.28), 121 (25.48), 94 (21.56), 82 (53.72), 81 (45.28), 72 (19.0), 53 (18.46), 43 (base).

4-(3-Furyl)butane-1,2-diol (47). A solution of **46** (1.00 g, 5.10 mmol) in THF–1 N HCl (1:1, 5 mL) was stirred at room temperature for 12 h. The mixture was neutralized by the addition of solid $NaHCO_3$ (0.5 g) and saturated with NaCl. The mixture was extracted with ether (3 × 50 mL), and the combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo to provide 0.51 g, 64%, of a yellow liquid which was used without further purification: ^1H NMR (60 MHz) δ 7.21 (t, J = 2 Hz, 1 H), 7.12 (m, 1 H), 6.12 (br s, 1 H), 3.50 (m, 5 H), 2.55 (t, J = 8 Hz, 2 H), 1.83 (br t, J = 8 Hz, 2 H); IR (neat) 3400 br, 2930, 1500, 1450, 1155, 1060 br, 915, 880, 790 cm^{-1}; EI/MS (70 eV) 156 (M^+, 9.37), 107 (5.50), 95 (11.22), 82 (70.1), 81 (base).

4-(3-Furyl)butane-1,2-diol 1-*p*-Toluenesulfonate (48). To a solution of alcohol **47** (0.51 g, 3.2 mmol) in pyridine (5 mL) cooled to 0 °C in an ice–water bath was added *p*-toluenesulfonyl chloride (0.61 g, 3.2 mmol) and the resulting mixture was stirred at 0 °C for 6 h. The mixture was then cast into ice–1 N aqueous HCl (30 g, 30 mL) and the solution extracted with ether (100 mL). The organic layer was washed with 1 N HCl (100 mL), water (100 mL), and brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo to provide 0.84 g, 84%, of a viscous orange liquid which was used without further purification: ^1H NMR (60 MHz) δ 7.68 (m, 2 H), 7.21 (m, 3 H), 6.18 (br s, 1 H), 3.93 (br s, 1 H), 3.74 (m, 3 H), 2.68 (m, 2 H), 2.35 (s, 3 H), 1.85 (m, 2 H); IR (neat) 3500 br, 2980, 2875, 1595, 1500, 1440, 1370, 1185, 1100, 990, 875, 820 cm^{-1}; EI/MS (70 eV) 310 (M^+, 4.91), 155 (12.78), 138 (33.87), 120 (21.06), 107 (10.71), 94 (50.85), 81 (base).

4-(3-Furyl)-1,2-epoxybutane (12b). To a suspension of NaH (0.13 g, 2.7 mmol, 50% in oil washed with 5 × 1 mL of dry hexane) in THF (5 mL) was added a solution of **48**, (0.84 g, 2.7 mmol) in THF (5 mL) over a period of 5 min. The resulting mixture was heated under reflux for 2 h. The mixture was allowed to cool to room temperature and was cast into water (50 mL) and ether (50 mL). The organic phase was separated, washed with brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo to yield a yellow liquid. The crude product was purified by chromatography on a column of silica gel (230–400 mesh, 30 g, 20 mm od, ether–petroleum ether 1:4, 20-mL fractions) by using the flash technique. Fractions 11–15 provided 0.350 g, 94%, of **12b** as a clear colorless liquid: ^1H NMR (250 MHz) δ 7.39 (t, J = 1.8 Hz, 1 H), 7.22 (m, 1 H), 6.23 (br s, 1 H), 2.98 (m, 1 H), 2.78 (t, J = 4.8 Hz, 1 H), 2.57 (m, 2 H), 2.48 (dd, J = 4.8 Hz, 1 H), 1.77 (m, 2 H); IR (neat) 2990, 2910, 2860, 2150, 1500, 1450, 1160, 1065, 1025, 910, 870, 780, 720 cm^{-1}; EI/MS (70 eV) 138 (M^+, 18.87), 107 (35.28), 94 (21.23), 81 (base). Anal. Calcd for $C_8H_{10}O_2$: C, 69.56; H, 7.24. Found: C, 69.49; H, 7.33.

General Procedure for Cyclization with BF_3·OEt_2. Preparation of 7,7-Dimethyl-6-hydroxy-4,5,6,7-tetrahydrobenzofuran (22). To a solution of **13** (0.1 g, 0.60 mmol) in CH_2Cl_2 (10 mL) cooled to −25 °C in a dry ice–carbon tetrachloride bath was added freshly distilled boron trifluoride etherate (0.028 g, 0.20 mmol). After the mixture had stirred for 5 min at −25 °C it was quenched with saturated aqueous NH_4Cl (10 mL). The mixture was cast into ether (50 mL) and the organic phase was separated, washed with water (50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo to yield a dark red liquid. The crude product was purified by chromatography on a column of silica gel (230–400 mesh, 40 g, 30 mm od, ether–petroleum ether 1:1, 10-mL fractions) by using the flash technique. Fractions 14–17 provided 47 mg, 47%, of **22** as a viscous colorless liquid which affords a white solid on cooling: ^1H NMR (250 MHz) δ 7.26 (d, J = 1.8 Hz, 1 H), 6.14 (d, J = 1.8 Hz, 1 H), 3.83 (br s, 1 H), 3.40 (td, J = 8, 6 Hz, 2 H), 1.92 (m, 2 H), 1.38 (s, 3 H), 1.22 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 155.8, 141.4, 114.4, 109.9, 76.3, 37.7, 28.0, 25.5, 21.1, 18.9; IR (neat) 3435 (br), 2900, 1620, 1500, 1470, 1385, 1360, 1280, 1150, 1120, 1085, 1045, 890, 780 cm^{-1}; EI/MS (70 eV) 166 (M^+, 40.4), 151 (9.4), 133 (4.80), 122 (base). Anal. Calcd for $C_{10}H_{16}O_2$: C, 72.29; H, 8.43. Found: C, 72.18; H, 8.54.

General Procedure for Cyclization with $EtAlCl_2$. Preparation of 22 and 2-Methyl-6-(3-furyl)-3-hydroxyhex-1-ene (23). To a solution of **13** (0.1 g, 0.6 mmol) in CH_2Cl_2 (10 mL) cooled to −78 °C in dry ice–2-propanol bath was added $EtAlCl_2$ (0.82 mL, 1.2 mmol, 1.47 M in hexane). The mixture was then warmed slowly to −25 °C (dry ice–carbon tetrachloride). The solution was stirred at −25 °C for 30 min and then quenched by the addition of saturated aqueous NH_4Cl (10 mL). The mixture warmed to room temperature and cast into ether (50 mL). The organic phase was separated, washed with 1 N aqueous HCl (50 mL), water (50 mL), and brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo to provide a yellow liquid. The crude product was purified by chromatography on a column of silica gel (230–400 mesh, 40 g, 30 mm od, ether–petroleum ether 1:1, 10-mL fractions) by using the flash technique. Fractions 9–12 provided 0.057 g, 57%, of **23** as a clear colorless liquid: ^1H NMR (250 MHz) δ 7.23 (t, J = 2 Hz, 1 H), 7.16 (m, 1 H), 6.19 (br s, 1 H), 4.88 (br s, 1 H), 4.76 (br s, 1 H), 4.0 (br s, 1 H), 3.38 (m, 1 H), 2.36 (m, 2 H), 1.98 (m, 2 H), 1.78 (s, 3 H); IR (neat) 3450 (br), 2990, 2900, 1500, 1470, 1385, 1290, 1160, 1085, 890, 780 cm^{-1}; EI/MS (70 eV) 166 (M^+, 9.7), 135 (base), 82 (47). Fractions 15–18 gave 0.022 g, 22%, of **22**.

General Procedure for Cyclization with Et_2AlCl. Preparation of 22 and 23. To a solution of **13** (0.10 g, 0.60 mmol) in CH_2Cl_2 (10 mL) cooled to 0 °C in an ice–water bath was added Et_2AlCl (0.82 mL, 1.2 mmol, 1.48 M in hexane) and the mixture immediately turned yellow. The solution was stirred at 0 °C for 1 h and then was cast into saturated aqueous NH_4Cl (50 mL) and ether (50 mL). The organic phase was separated, washed with 1 N aqueous HCl (50 mL), water (50 mL), and brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo to yield a yellow liquid. Flash chromatography of the crude product provided 0.049 g, 49%, of **23** and 0.022 g, 22%, of **22**.

General Procedure for Cyclization with Alumina. Preparation of 22 and 23. To a solution of **13** (0.1 g, 0.60 mmol) in dry hexane (15 mL) was added basic alumina (2.0 g, activity I) and the suspension was stirred at room temperature for 24 h. Methanol (10 mL) was added, the mixture was filtered, and the alumina rinsed with methanol (25 mL). The solvent was removed in vacuo to yield a colorless liquid. Flash chromatography of the crude product provided 0.032 g, 32%, of **22** and 0.051 g, 51%, of **23**.

General Procedure for Cyclization with Ti(O-*i*-Pr)$_3$Cl. Preparation of 22. To a solution of **13** (0.10 g, 0.60 mmol) in CH_2Cl_2 (10 mL) was added Ti(O-*i*-Pr)$_3$Cl[23,37] (2.40 mL, 1.8 mmol, 0.75 M in CH_2Cl_2). The solution was allowed to stir at room temperature for 2 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (10 mL) and the resulting two phase mixture was cast into saturated aqueous NH_4Cl (50 mL) and ether (50 mL). The organic phase was separated, washed with 1 N aqueous HCl (50 mL), water (50 mL), and brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo to yield a light yellow liquid. Flash chromatography of the crude product provided 0.078 g, 78%, of **22**.

General Procedure for Cyclization with ZnI_2. Preparation of 22. To a solution of **13** (0.1 g, 0.50 mmol) in CH_2Cl_2 (10 mL) was added anhydrous sodium acetate (50 mg, 0.60 mmol) followed immediately by ZnI_2·OEt_2[38] (0.70 g, 1.8 mmol). The resulting mixture was stirred in the dark for 3 h. The mixture was then cast into saturated aqueous NH_4Cl (50 mL) and ether (50 mL). The organic phase was separated, washed with 10% aqueous sodium bisulfite (50 mL), water (50 mL), and brine (50 mL), dried (50 mL), and concentrated in vacuo to provide a yellow liquid. Flash chromatography of the crude product provided 0.071 g, 71%, of **22**.

Attempted Cyclization of Epoxy Furan 11 with BF_3·OEt_2. A solution of **11** (0.10 g, 0.66 mmol) in CH_2Cl_2 (10 mL) was reacted with BF_3·OEt_2 (0.031 g, 0.22 mmol) according to the general procedure for cyclization with BF_3·OEt_2. The crude product was purified by chromatography on a column of silica gel (230–400 mesh, 40 g, 30 mm od, ether–petroleum ether, 1:1, 10-mL fractions) by using the flash technique. Fractions 10–14 provided 0.062 g, 62%, of **18** as a clear colorless liquid: ^1H NMR (250 MHz) δ 7.34 (t, J = 2 Hz, 1 H), 7.24 (m, 1 H), 6.28 (br s, 1 H), 4.90 (br s, 1 H), 4.79 (br s, 1 H), 3.60 (m, 1 H), 2.48 (d, J = 7.2 Hz, 2 H), 1.53

(37) Reetz, M. T.; Peter, R. *Tetrahedron Lett.* **1981**, *22*, 4691.
(38) Brauer, Georg., Ed. "Handbook of Preparative Inorganic Chemistry"; Academic Press: New York, 1965; p 1017.

(s, 3 H); IR (neat) 3500 (br), 3000, 2980, 1500, 1495, 1170, 1080, 1025, 915, 870, 780 cm^{-1}; EI/MS (70 eV) 152 (M^+, 3.7), 137 (23.4), 117 (8.3), 81 (base).

Attempted Cyclization of Epoxy Furan 11 with Et_2AlCl. A solution of 11 (0.1 g, 0.66 mmol) in CH_2Cl_2 (10 mL) was treated with Et_2AlCl (0.90 mL, 1.32 mmol, 1.47 M in hexane) according to the general procedure for cyclization with Et_2AlCl to provide 0.085 g, 85%, of 18.

Attempted Cyclization of Epoxy Furan 11 with Alumina. A solution of 11 (0.1 g, 0.66 mmol) in dry hexane (10 mL) was treated with 2.0 g of alumina according to the general procedure for cyclization with alumina to provide 0.083 g, 83%, of 18.

Attempted Cyclization of Epoxy Furan 12a with BF_3·OEt_2. A solution of **12a** (0.10 g, 0.66 mmol) in CH_2Cl_2 (10 mL) was treated with BF_3·OEt_2 (0.031 g, 0.22 mmol) according to the general procedure for cyclization with BF_3·OEt_2. The crude product was purified by chromatography on a column of silica gel (230–400 mesh, 40 g, 30 mm od, ether–petroleum ether 1:1, 10-mL fractions) by using the flash technique. Fractions 9–12 provided 0.053 g, 53%, of **20** as a mixture of isomers: ^1H NMR (60 MHz) δ 7.26 (t, J = 2 Hz, 1 H), 7.18 (m, 1 H), 6.21 (br s, 1 H), 5.48 (m, 0.5 H), 4.94 (s, 0.5 H), 4.83 (s, 0.5 H), 4.0 (br s, 1 H), 3.49 (br s, 1 H), 3.12 (d, J = 6 Hz, 2 H), 2.40 (m, 4 H), 1.86 (s, 1.5 H); IR (neat) 3450 (br), 2990, 2980, 2780, 1500, 1380, 1165, 1070, 1030, 925, 880, 790 cm^{-1}; EI/MS (70 eV) 152 (M^+, 5.3), 137 (17.6), 121 (41.3), 106 (10.9), 82 (base).

Attempted Cyclization of Epoxy Furan 12b with BF_3·OEt_2. A solution of **12b** (0.10 g, 0.73 mmol) in CH_2Cl_2 (10 mL) was reacted with BF_3·OEt_2 (0.034 g, 0.24 mmol) according to the general procedure for cyclizations with BF_3·OEt_2. The crude product was purified by chromatography on a column of silica gel (230–400 mesh, 40 g, 30 mm od, ether–petroleum ether, 1:1, 10-mL fractions) by using the flash technique. Fractions 10–12 provided 0.049 g, 49%, of **21** as a mixture of isomers: ^1H NMR (250 MHz) δ 7.35 (t, J = 2 Hz, 1 H), 7.22 (m, 1 H), 6.22 (br s, 1 H), 4.58 (m, 2 H), 3.30 (m, 2 H), 2.54 (m, 2 H); IR (neat) 3450 (br), 2995, 2890, 1500, 1410, 1150, 1090, 1015, 890, 780 cm^{-1}; EI/MS (70 eV) 138 (M^+, 28.8), 121 (14.4), 95 (21.7), 81 (base).

Cyclization of Epoxy Furan 12b with ZnI_2·OEt_2. Preparation of 21 and 6-(Hydroxymethyl)-4,5-dihydro-6*H*-cyclopenta[*b*]furan (19b). A solution of **12b** (0.10 g, 0.73 mmol) in CH_2Cl_2 (10 mL) was reacted with ZnI_2·OEt_2 (0.86 g, 2.19 mmol) and sodium acetate (60 mg, 0.73 mmol) according to the general procedure for cyclization with ZnI_2·OEt_2. The crude product was purified by chromatography on a column of silica gel (230–400 mesh, 40 g, 30 mm od, ether–petroleum ether, 1:1, 10-mL fractions) by using the flash technique. Fraction 8–11 provided 0.044 g, 44%, of **21** and fractions 13–14 provided 0.025 g, 25%, of **19b** as a clear colorless liquid: ^1H NMR (250 MHz) δ 7.22 (d, J = 1.8 Hz, 1 H), 6.41 (d, J = 1.8 Hz, 1 H), 3.19 (m, 2 H), 2.78 (m, 5 H); IR (neat) 3480 (br), 2900, 1500, 1425, 1120, 1080, 1050, 1010, 890, 780 cm^{-1}; EI/MS (70 eV) 138 (M^+, 23.4), 121 (8.3), 109 (8.51), 94 (base). Anal. Calcd for $C_8H_{10}O_2$: C, 69.56; H, 7.24. Found: C, 69.54; H, 7.27.

Cyclization of Epoxy Furan 14 with BF_3·OEt_2. Preparation of 7-Methyl-7-(hydroxymethyl)-4,5,6,7-tetrahydrobenzofuran 24 and Alcohols 25. A solution of **14** (0.10 g, 0.60 mmol) in CH_2Cl_2 (10 mL) was reacted with BF_3·OEt_2 (0.28 g, 0.20 mmol) according to the general procedure for cyclization with BF_3·OEt_2. The crude product was purified by chromatography on a column of silica gel (230–400 mesh, 40 g, 30 mm od, ether petroleum–ether, 1:1, 10-mL fractions) by using the flash technique. Fractions 10–12 provided 0.01 g, 10%, of **25** as a mixture of isomers: ^1H NMR (250 MHz) δ 7.26 (t, J = 2 Hz, 1 H), 7.16 (m, 1 H), 6.19 (br s, 1 H), 5.52 (t, J = 8 Hz, 0.5 H), 4.90 (br s, 0.5 H), 4.82 (br s, 0.5 H), 3.56 (br s, 1 H), 2.36 (m, 5 H), 1.78 (s, 1.5 H); EI/MS (70 eV) 166 (M^+, 12.3), 151 (8.3), 135 (43.1), 120 (10.3), 94 (14.9), 82 (base). Fractions 13–17 provided 0.03 g, 30%, of **24** as a pale yellow liquid: ^1H NMR (250 MHz) δ 7.21 (d, J = 1.8 Hz, 1 H), 6.15 (d, J = 1.8 Hz, 1 H), 3.52 (s, 2 H), 2.38 (m, 2 H), 1.96 (m, 2 H), 1.24 (s, 3 H); IR (neat) 3440 (br), 2940, 1500, 1380, 1205, 1160, 1040, 890, 740 cm^{-1}; EI/MS (70 eV) 166 (M^+, 8.8), 149 (4.4), 135 (base). Anal. Calcd for $C_{10}H_6O_2$: C, 72.29; H, 8.43. Found: C, 71.96; H, 8.51.

Attempted Cyclization of Epoxy Furan 15 with BF_3·OEt_2. Preparation of 2-Methyl-6-(3-furyl)-3-hydroxyhex-1-ene (27). A solution of **15** (0.10 g, 0.55 mmol) in CH_2Cl_2 (10 mL) was treated with BF_3·OEt_2 (0.025 g, 0.18 mmol) according to the general procedure for cyclization with BF_3·OEt_2. The crude product was purified by chromatography on a column of silica gel (230–400 mesh, 70 g, 40 mm od, ether–petroleum ether, 1:1, 25-mL fractions) by using flash technique. Fractions 11–13 provided 0.041 g, 41%, of **27**: ^1H NMR (60 MHz) δ 7.39 (t, J = 2 Hz, 1 H), 7.21 (m, 1 H), 6.24 (br s, 1 H), 4.85 (s, 1 H), 4.80 (s, 1 H), 4.10 (m, 1 H), 3.62 (br s, 1 H), 2.60 (m, 2 H), 2.44 (m, 4 H), 1.61 (s, 3 H); IR (neat) 3450 (br), 2990, 1500, 1450, 1390, 1290, 1150, 1090, 890, 780 cm^{-1}; EI/MS (70 eV) 180 (M^+, 10.6), 162 (8.3), 139 (28.3), 94 (43.2), 82 (base).

Cyclization of Epoxy Furan 15 with Et_2AlCl. Preparation of 8,8-Dimethyl-7-hydroxy-4,5,7,8-tetrahydro-6*H*-cyclohepta[*b*]furan 26 and 27. A solution of **15** (0.10 g, 0.55 mmol) in CH_2Cl_2 (10 mL) was treated with Et_2AlCl (0.75 mL, 1.10 mmol, 1.47 M in hexane) according to the general procedure for cyclization with Et_2AlCl. The crude product was purified by chromatography on a column of silica gel (230–400 mesh, 45 g, 30 mm od, ether–petroleum ether, 1:1, 10-mL fractions) by using the flash technique. Fractions 9–12 provided 0.069 g, 69%, of **27** and fractions 15–17 provided 0.01 g, 10%, of **26** as a pale yellow liquid: ^1H NMR (250 MHz) δ 7.24 (d, J = 1.8 Hz, 1 H), 6.13 (d, J = 1.8 Hz, 1 H), 3.73 (t, J = 4.2 Hz, 1 H), 2.47 (m, 2 H), 1.91 (m, 6 H), 1.30 (s, 3 H), 1.22 (s, 3 H); IR (neat) 3430 (br), 2980, 1620, 1500, 1470, 1380, 1360, 1285, 1160, 1115, 1090, 1030, 890, 730 cm^{-1}; EI/MS (70 eV) 180 (M^+, 5.28), 166 (32.2), 151 (12.6), 149 (17.9), 122 (base). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.33; H, 8.89. Found: C, 73.32; H, 8.83.

Cyclization of Epoxy Furan 16 with BF_3·OEt_2. Preparation of 8-Methyl-8-(hydroxymethyl)-4,5,7,8-tetrahydro-6*H*-cyclohepta[*b*]furan 28 and 29. A solution of **16** (0.10 g, 0.55 mmol) in CH_2Cl_2 (10 mL) was treated with BF_3·OEt_2 (0.025 g, 0.18 mmol) according to the general procedure for cyclization with BF_3·OEt_2. The crude product was purified by chromatography on a column of silica gel (230–400 mesh, 40 g, 30 mm od, ether–petroleum ether 1:1, 10-mL fractions) by using the flash technique. Fractions 9–12 provided 0.012 g, 12%, of **29** as a mixture of isomers: ^1H NMR (250 MHz) δ 7.28 (t, J = 2 Hz, 1 H), 7.16 (br s, 1 H), 6.18 (br s, 1 H), 4.96 (s, 0.5 H), 4.80 (s, 0.5 H), 4.10 (m, 0.5 H), 3.10 (br s, 1 H), 3.28 (m, 2 H), 2.86 (m, 2 H), 2.23 (m, 5 H), 1.83 (s, 1.5 H); IR (neat) 3450 (br), 2900, 1500, 1460, 1320, 1290, 1160, 1075, 780 cm^{-1}; EI/MS (70 eV) 180 (M^+, 9.2), 165 (10.5), 149 (23.6), 139 (10.3), 94 (32.6), 82 (base). Fractions 14–16 provided 0.010 g, 10%, of **28** as a clear liquid: ^1H NMR (250 MHz) δ 7.17 (d, J = 1.8 Hz, 1 H), 6.12 (d, J = 1.8 Hz, 1 H), 3.79 (d, J = 11.1 Hz, 1 H), 3.58 (d, J = 11.1 Hz, 1 H), 2.47 (m, 2 H), 1.96–1.31 (br m, 6 H), 1.22 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 155.6, 141.1, 113.9, 109.8, 76.6, 37.7, 28.0, 25.7, 21.3, 19.0; IR (neat) 3470 (br), 2920, 1500, 1460, 1385, 1290, 1210, 1165, 1090, 890, 780 cm^{-1}; EI/MS (70 eV) 180 (M^+, 10.0), 150 (11.7), 149 (base). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.33; H, 8.89. Found: C, 73.40; H, 8.99.

Cyclization of Epoxydendrolasin (39) with Ti(O-*i*-Pr)$_3$Cl. Preparation 3β-Hydroxypallescensin A (49). A solution of epoxydendrolasin (**39**)[10] (0.20 g, 0.85 mmol) in CH_2Cl_2 (10 mL) was treated with Ti(O-*i*-Pr)$_3$Cl (3.4 mL, 2.55 mmol, 0.75 M in CH_2Cl_2) according to the general procedure for cyclization with Ti(O-*i*-Pr)$_3$Cl. The crude product was purified by chromatography on a column of silica gel (230–400 mesh, 70 g, 50 mm od, ether–petroleum ether 1:3, 25-mL fractions) by using flash technique. Fractions 16–19 provided 0.124 g, 62%, of **49** as a white solid: mp 120–122 °C (lit.[29] mp 122–122.5 °C); ^1H NMR (250 MHz) δ 7.13 (d, J = 1.8 Hz, 1 H), 6.02 (d, J = 1.8 Hz, 1 H), 3.31 (m, 3 H), 3.43 (m, 4 H), 2.22 (m, 1 H), 1.5–2.1 (m, 4 H), 1.18 (s, 3 H), 1.07 (s, 3 H), 0.89 (m, 3 H); EI/MS (70 eV) 234 (M^+, 46.6), 219 (82), 201 (base).

Acknowledgment. We gratefully acknowledge support of this research by the Camille and Henry Dreyfus Foundation, the Research Corporation, the Petroleum Research Fund administered by the American Chemical Society, and Michigan State University.

Registry No. 11, 87452-80-0; 12a, 87452-81-1; 12b, 87452-82-2; 13, 61597-52-2; 14, 87461-59-4; 15, 87452-83-3; 16, 87452-84-4; 18, 87452-85-5; 19b, 87452-86-6; 20 (terminal alkene), 87452-87-7; 20

(internal alkene), 87453-10-9; (*E*)-**21**, 87452-88-8; (*Z*)-**21**, 87453-11-0; **22**, 87452-89-9; **23**, 56694-87-2; **24**, 87452-90-2; **25** (terminal alkene), 87452-91-3; **25** (internal alkene), 87453-12-1; **26**, 87452-92-4; **27**, 87452-93-5; **28**, 87452-94-6; **29** (terminal alkene), 87452-95-7; **29** (internal alkene), 87453-13-2; **33**, 87452-96-8; **34**, 87452-97-9; **35**, 539-52-6; **36**, 87452-98-0; **37**, 87452-99-1; **38**, 87453-00-7; (*E*)-**39**, 83670-82-0; **40**, 624-57-7; **41a**, 87453-01-8; **41b**, 87453-02-9; **42a**, 87453-03-0; **42b**, 87453-04-1; **43**, 87453-05-2; **44**, 87453-06-3; **45**, 4351-11-5; **46**, 87453-07-4; **47**, 87453-08-5; **48**, 87453-09-6; (±)-**49**, 73191-64-7; (±)-**50**, 73210-04-5; BF_3·OEt_2, 109-63-7; $EtAlCl_2$, 563-43-9; Et_2AlCl_2, 96-10-6; Al_2O_3, 1344-28-1; $Ti(OiPr)_3Cl$, 20717-86-6; ZnI_2, 10139-47-6; (3-furyl)chloromethane, 14497-29-1; 1-bromo-2-methylpropene, 3017-69-4; 3-chloro-2-methylpropene, 563-47-3; 4-chloro-2-methyl-2-butene, 503-60-6; 4-iodo-2-methyl-1-butene, 53750-52-0; 5-iodo-2-methyl-2-pentene, 43161-11-1; (*E*)-epoxygeranyl chloride, 43119-82-0.

α-Oxo Sulfones.[1] 4. Correction of a Pretended α-Oxo Sulfone by an Unambiguous Synthesis of the Revised Structure

K. Schank,[†] A. Frisch,[†] and B. Zwanenburg*

Departments of Organic Chemistry, University of Saarland, D-6600 Saarbrücken, Federal Republic of Germany, and University of Nijmegen, Toernooiveld, 6525 ED Nijmegen, The Netherlands

Received March 29, 1983

By an independent synthesis the oxidation product of 1,1-dichloro-2,2-dimethyl-1-(phenylthio)-3-butene (**1**) was shown not to be α-oxo sulfone "**2**" as published earlier but a phenylsulfonyl γ-butyrolactone, **3**. This synthesis involves the intramolecular reaction of a sulfenic carboxylic mixed anhydride with an olefinic bond. A rationale for the formation of **3** from **1** is presented.

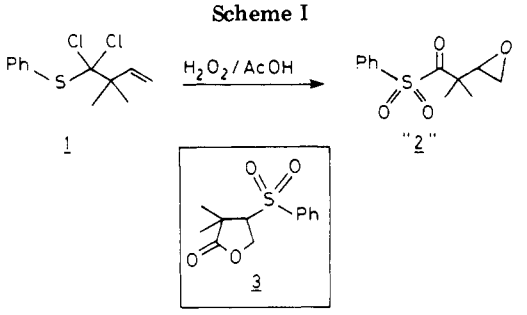
α-Diketones and α-disulfones are both stable and well-defined structures. In contrast, only a few isolable and well-characterized examples of α-oxo sulfones have been described.[2] Recently, several reports dealing with α-oxo sulfones were critically reviewed by us.[2] In many instances the suggested α-oxo sulfone structure was proven to be incorrect or at least questionable. In this context our attention[3] was drawn to the oxidation of 1,1-dichloro-2,2-dimethyl-1-(phenylthio)-3-butene (**1**) with hydrogen peroxide (30%) in acetic acid, giving aliphatic α-oxo sulfone "**2**" (Scheme I).[4]

In view of our experience[1] with established α-oxo sulfones the reported properties[4] were not in line with those expected for **2**. First, the high stability toward hydrolysis is incompatible with structure **2** as α-oxo sulfones are very sensitive to water.[1] Second, the IR absorption at 1790 cm^{-1} is not typical for an α-oxo sulfone (~1700 cm^{-1})[2] but rather is suggestive of a γ-lactone. One of us (B.Z.)[5] proposed on the basis of the provided spectral data the γ-lactone structure **3** as a possible alternative for "**2**". The aim of this investigation is to devise an unambiguous synthesis for **3** and to establish the true nature of the product "**2**" obtained by Parham and Groen.[4]

First of all we ensured that the reported[4] preparation of "**2**" could be repeated. This was found to be the case; even the yield of "**2**" could be considerably improved by a slight modification of the procedure.

The synthetic plan for lactone **3** is outlined in Scheme II. The essential feature of this sequence is that dimethylvinylacetic acid **7** is transformed into the carboxylic sulfenic mixed anhydride **8**. The formation of such (unstable) mixed anhydrides has been reported previously.[7] These species react with olefinic double bonds in a similar fashion[7,8] as is known for sulfenyl halides.[9] It should be noted that this proposed lactone formation in fact resembles the iodolactonization of the sodium salt of **7** with iodine which leads to the corresponding 3-iodo-2,2-dimethyl-γ-butyrolactone.[10]

Scheme I



Treatment of carboxylic acid[11] **7**, prepared by an improved procedure (see Scheme III and the Experimental

(1) For α-oxo sulfones **3**, see: Schank, K.; Werner, F. *Liebigs Ann. Chem.* **1980**, 1477.
(2) Schank, K.; Werner, F. *Liebigs Ann. Chem.* **1979**, 1977.
(3) We (K.S. and A.F.) are obliged to Dr. H.-G. Schmitt from Bayer AG, Leverkusen (FRG), for bringing ref 4a to our attention.
(4) (a) Parham, W. E.; Groen, S. H. *J. Org. Chem.* **1966**, *31*, 1694. (b) Groen, S. H. Thesis, University of Groningen, The Netherlands, 1966.
(5) Ph.D. ceremony of S. H. Groen, University of Groningen, The Netherlands, March 4, 1966.
(6) We first tried to prepare lactone **3** from methallyl phenyl sulfone. Isomerization to an α,β-unsaturated sulfone and simultaneous conjugate addition of cyanide by treatment with sodium hydrogen carbonate and sodium cyanide in ethanol at 80 °C for 3 days gave 2,2-dimethyl-3-(phenylsulfonyl)propanenitrile (yield 40%; mp 87–90 °C). Subsequent methanolysis (methanol/HCl/-20 °C) followed by hydrolysis (methanol/KOH/20 °C) led to 2,2-dimethyl-3-(phenylsulfonyl)propanoic acid (yield 62%; mp 142 °C). Attempts to ring close this compound via reaction of its dilithio derivative with methylene iodide failed. Presumably, the carbon atom α to the sulfonyl group is too sterically shielded for an alkylation reaction.
(7) (a) Havlik, A. J.; Kharash, N. *J. Am. Chem. Soc.* **1956**, *78*, 1207. (b) Brydon, A.; Cameron, G. G.; Hogg, D. R. *Int. J. Sulfur Chem., Part A* **1972**, *A2*, 289. (c) Putnam, R. E.; Sharkey, W. H. *J. Am. Chem. Soc.* **1957**, *79*, 6526. (d) Bell, P. A.; Hogg, D. R.; Robertson, A. *J. Chem. Soc., Perkin Trans 1* **1978**, 1246.
(8) One could argue that conversion of **7** to **9** may be envisaged without the intermediacy of **8**. However, the carboxylate of **7** is probably a better nucleophile with regard to benzenesulfenyl chloride than the olefin. The intermediate **8** is relevant in understanding the formation of **3** from **1** (Scheme III).
(9) Kühle, E. "The Chemistry of the Sulfenic Acids"; Georg Thieme Verlag: Stuttgart, 1973; pp 44–52.
(10) Bougault, J. *Ann. Chim. Phys.* **1908**, *14* (8), 145, 166.

*Address correspondence to the University of Nijmegen.
[†]University of Saarland.

0022-3263/83/1948-4580$01.50/0